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(54) Covalently bound dimers of glycopetide antibiotics

(57) The present invention is directed to certain glycopeptide dimers in which two glycopeptide units are covalently linked to one another through their disaccharide amine, via a linking radical. This invention is also directed to the monomeric intermediates. All of these compounds are useful as antibacterials, especially for the control of gram positive bacteria; the compounds are particularly useful for the control of resistant bacterial strains, such as vancomycin-resistant-enterococci ("VRE").

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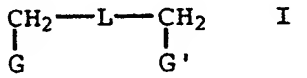
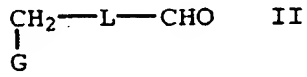
Description

The present invention is directed to certain glycopeptide dimers in which two glycopeptide units are covalently linked to one another through their disaccharide amine, via a linking radical. This invention is also directed to the monomeric intermediates. All of these compounds are useful as antibacterials, especially for the control of gram positive bacteria; the compounds are particularly useful for the control of resistant bacterial strains, such as vancomycin-resistant-enterococci ("VRE") .

The compounds of the present invention are defined by the following Formulae I and II:

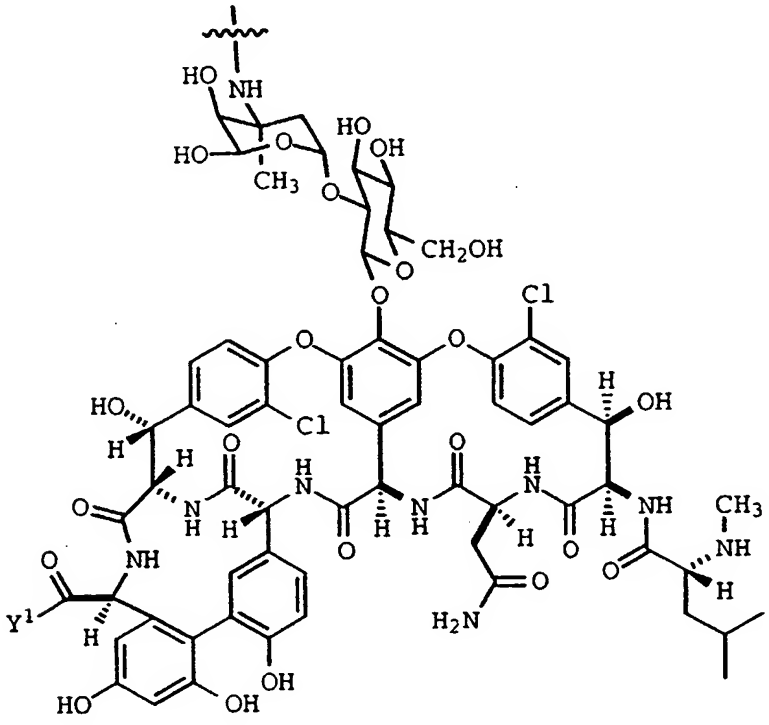


I

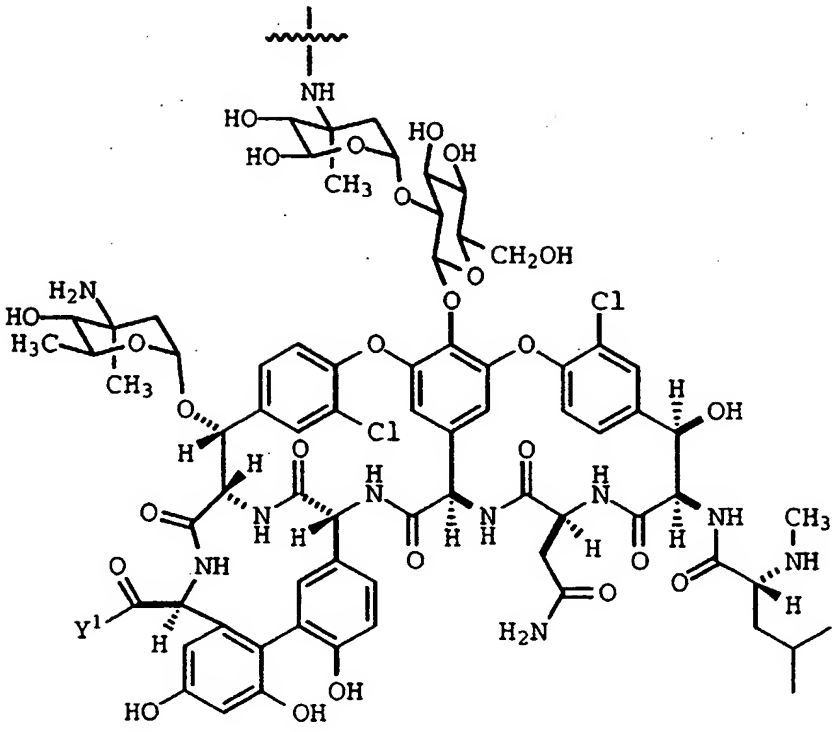


II

In the above formulae, each of G and G' is independently selected from the group consisting of deshydrovancomycin of the formula:



and deshydroA82846B of the formula:



wherein Y^1 is OH or

and Y^2 is defined as follows:

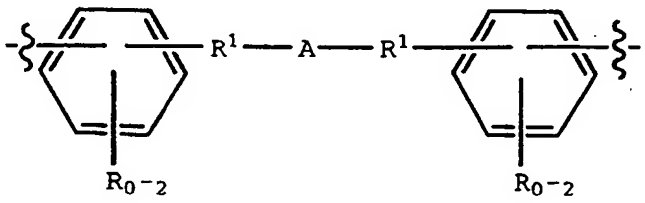
(1) each Y^2 independently represents

hydrogen,
alkyl of C_1-C_{10},
cycloalkyl of C_5-C_6,
cycloalkenyl of C_5-C_6,
naphthyl,
biphenylyl,
radical of the formula -Y^3-(Y^4)0, 1, or 2, wherein Y^3 is loweralkyl of C_1-C_6 optionally substituted by from one to three substituents, each of which is independently selected from the group consisting of halo, nitro, cyano, alkoxy, haloalkyl, and haloalkoxy; and Y^4 is

wherein each Y^5 is independently hydrogen or loweralkyl of C_1-C_4, or Y^4 is phenyl or phenyl substituted with from one to three substituents, each of which is independently
halo,
nitro,
loweralkyl of C_1-C_4,
cycloalkyl of C_5-C_6,

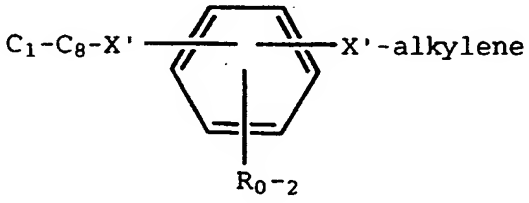
loweralkoxy of C_1-C_4,
halololoweralkyl of C_1-C_4, or
halololoweralkoxy of C_1-C_4; or

(2) one Y^2 is hydrogen and the other Y^2 is (2-furanon-3-yl); or
(3) both Y^2s are taken together with the nitrogen and constitute a five- to seven-membered heterocyclic ring optionally containing in addition to the indicated nitrogen atom one additional hetero ring atom which is nitrogen, oxygen, or sulfur, and which heterocyclic radical can be unsubstituted or substituted with from one or two substituents, each of which is loweralkyl of C_1-C_2, loweralkoxy of C_1-C_2, phenyl, benzyl, or C_1-C_6-alkanoyl; and L is a divalent linking radical of the formula A:

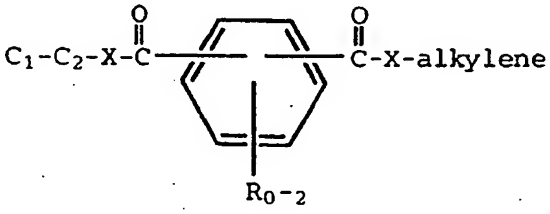
A. 

wherein A is:

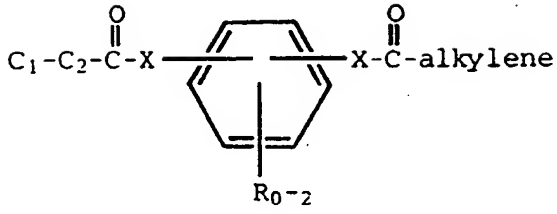
alkylene of C_1-C_{16},
(alkylene of C_1-C_4-X')$_q$-alkylene of C_1-C_4, wherein q is 1-3,
alkylene of



of C_1-C_8;
alkylene of



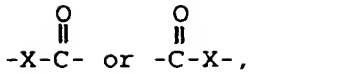
of C_1-C_2, or
alkylene of

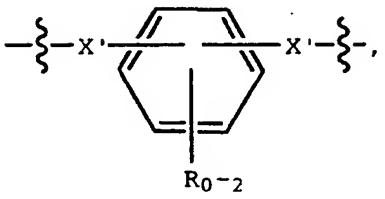


of C_1-C_2;

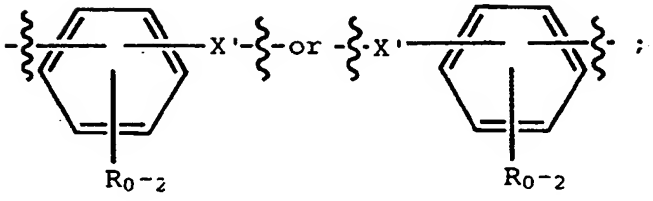
each R^1 is independently

CH_2,
O,
S,



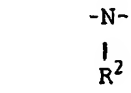


or



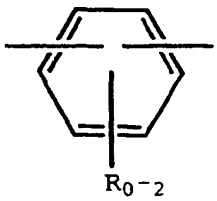
wherein each R independently represents halo, loweralkyl of C_1-C_6, loweralkoxy of C_1-C_6, phenyl, or phenyl substituted by from 1 to 2 substituents, each of which is independently halo, loweralkyl of C_1-C_6, or loweralkoxy of C_1-C_6; each X is independently -O- or

wherein R^2 is H or loweralkyl of C_1-C_4; and each X' is independently -O-, -S-, or



wherein R^2 is as defined above; or L is a divalent linking radical of the formula B:

B. -alkylene of C_1-C_8-R^3-X"-R^3-alkylene of C_1-C_8-wherein X" represents alkylene of C_1-C_4 or a phenylene of the formula



wherein R is as defined above; and each R^3 is independently CH_2 or O.

The present invention also includes salts of the foregoing compounds.

In compounds of Formula I, the glycopeptide units, G and G', may be identical or different. In compounds of both Formulae, linkage of the glycopeptide units is through the amine group of the disaccharide sugar. Any "alkylene" of C_2 or higher can be straight chain or branched.

Certain compounds of the present invention are preferred. Compounds of Formula I, and especially symmetrical compounds (G=G' and/or both R^1 are identical), are preferred for their more efficient synthesis.

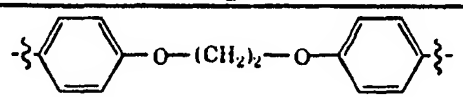
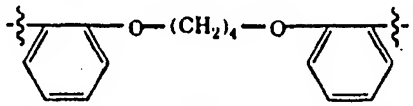
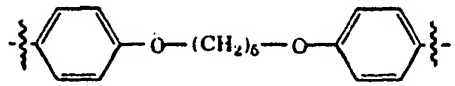
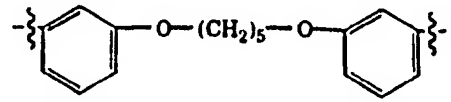
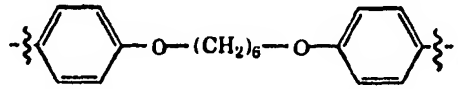
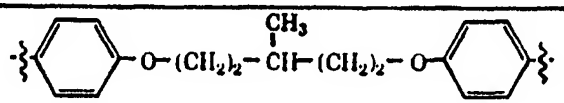
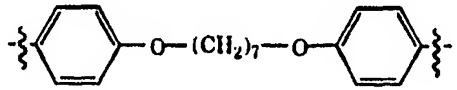
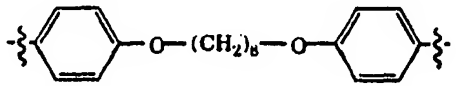
Antibacterial activity is enhanced by employing preferred "L" groups. Preferences include the following, individually and in any combination:

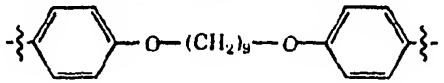
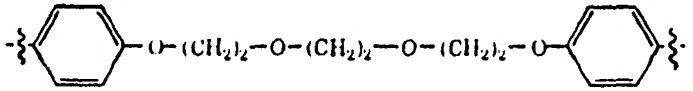
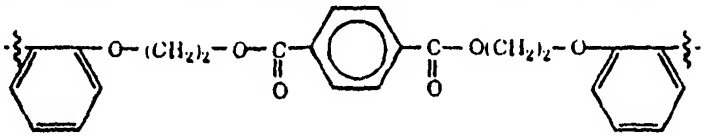
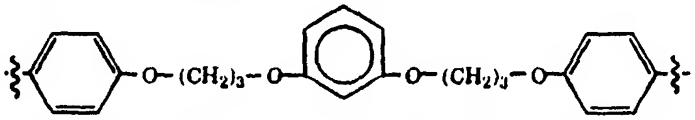
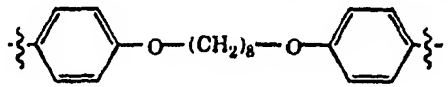
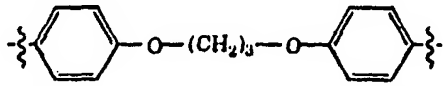
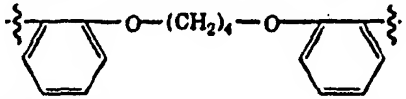
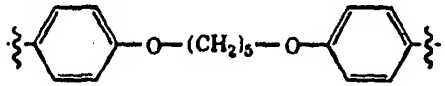
L = a linking radical of formula A
L = a linking radical of formula B wherein the carbon attached to -CH_2-G or to -CH_2-G' is branched
R^1 = O
A = alkylene of C_1-C_{16}, especially straight-chain and especially C_6-C_{12};
A = (alkylene of C_1-C_4-X')q-alkylene of C_1-C_4, especially wherein X'=O; the alkylene is -$(CH_2)_2$-; and q=2;
R = phenyl and substituted phenyl, especially chlorophenyl; and especially when R has this value on a phenyl ring within "A".

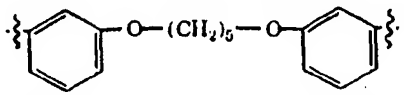
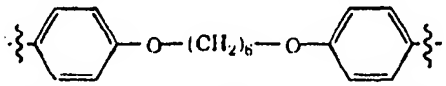
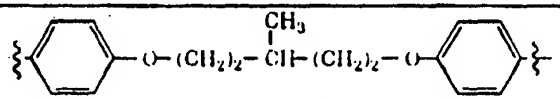
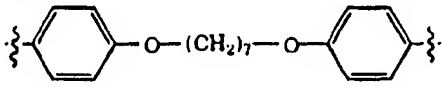
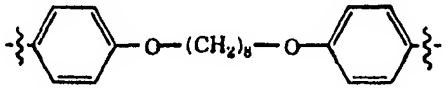
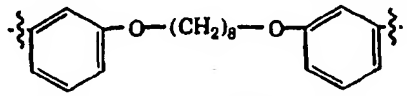
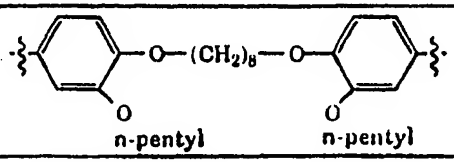
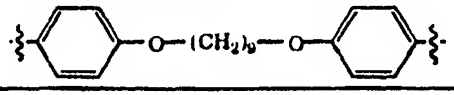
Other preferences will be apparent from the further teachings herein.

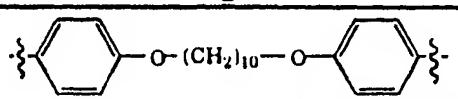
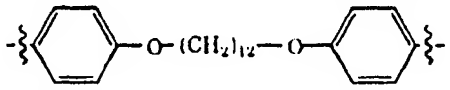
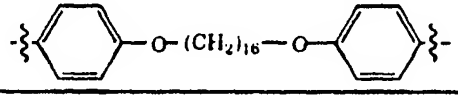
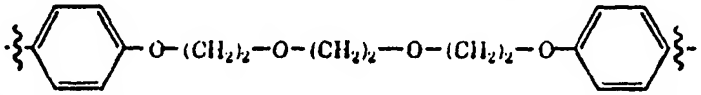
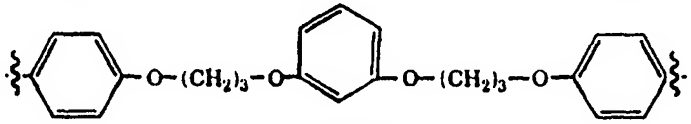
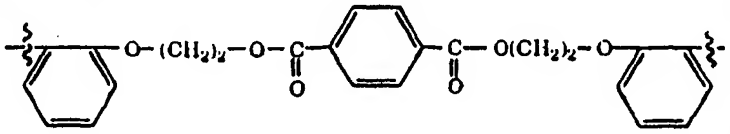
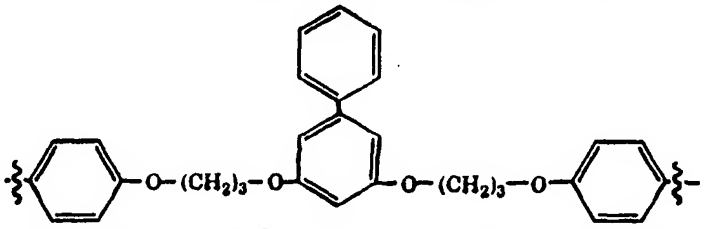
Representative compounds of the present invention are set forth in following TABLES 1 and 2. TABLE 1 identifies dimers of Formula I; TABLE 2 identifies compounds of Formula II.

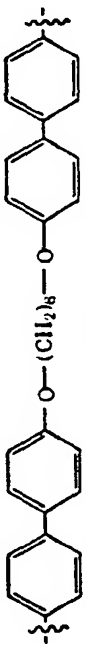
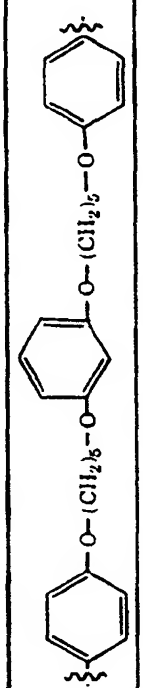
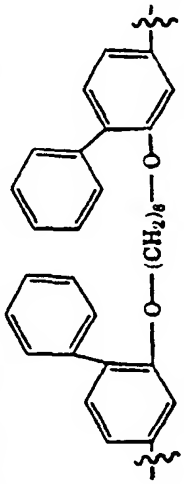
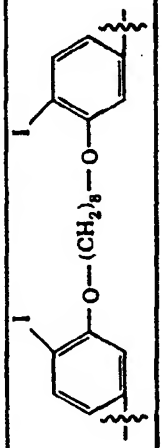
TABLE 1

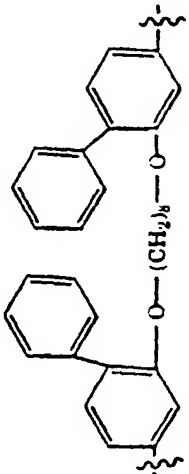
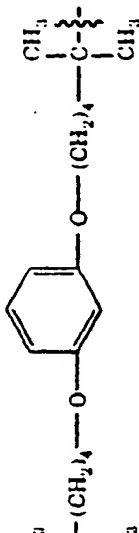
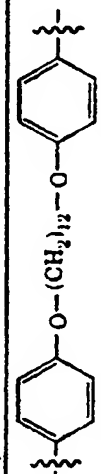
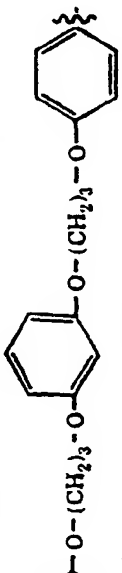
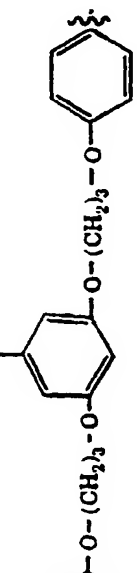
Ex. #	G	G'	L	Name
1	Vanco	Vanco		1,2-ethanediyl-bis-[(oxy-4,1-phenylene)methylene]-bis-[vancomycin]
2	Vanco	Vanco		1,4-butanediyl-bis-[(oxy-2,1-phenylene)-methylene]-bis-[vancomycin]
3	Vanco	Vanco		1,5-pentanediyl-bis-[(oxy-4,1-phenylene)methylene]-bis-[vancomycin]
4	Vanco	Vanco		1,5-pentanediyl-bis-[(oxy-3,1-phenylene)-methylene]-bis-[vancomycin]
5	Vanco	Vanco		1,6-hexanediyl-bis-[oxy-4,1-phenylene)-methylene]-bis-[vancomycin]
6	Vanco	Vanco		[3-methyl-1,5-pentanediyl-bis[(oxy-4,1-phenylene)-methylene]-bis-[vancomycin]
7	Vanco	Vanco		1,7-heptanediyl-bis-[oxy-4,1-phenylene)-methylene]-bis-[vancomycin]
8	Vanco	Vanco		1,8-octanediyl-bis-[(oxy-4,1-phenylene)-methylene]-bis-[vancomycin]

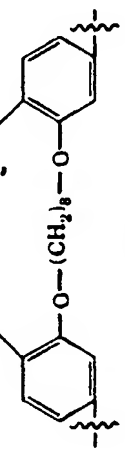
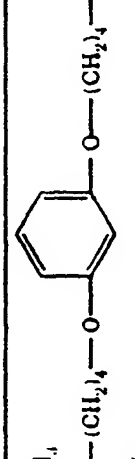
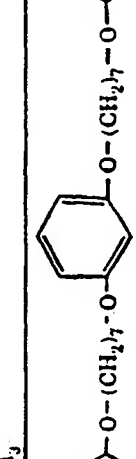
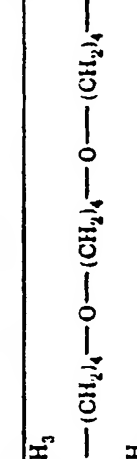
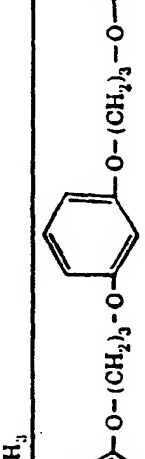
Ex. #	G	G'	L	Name
9	Vanco	Vanco		1,9-nonanediyl-bis-[(oxy-4,1-phenylene)-methylene]-bis-[vancomycin]
10	Vanco	Vanco		1,2-ethanediyl-bis-[oxy-1,2-ethyleneoxy-4,1-phenylene]-methylene]-bis-[vancomycin]
11	Vanco	Vanco		1,4-phenylene-bis-[(carbonyloxy-1,2-ethylene-oxy-2,1-phenylene)]-methylene]-bis-[vancomycin]
12	Vanco	Vanco		1,3-phenylene-bis-[(oxy-1,3-n-propyleneoxy-4,1-phenylene)]-methylene]-bis-[vancomycin]
13	A82846B	Vanco		1,8-octanediyl-bis-[(oxy-4,1-phenylene)-methylene]-[vancomycin][A82846B]
14	A82846B	A82846B		1,3-propanediyl-bis-[(oxy-4,1-phenylene)-methylene]-bis-[A82846B]
15	A82846B	A82846B		1,4-butanediyl-bis-[(oxy-2,1-phenylene)-methylene]-bis-[A82846B]
16	A82846B	A82846B		1,5-pentanediyl-bis-[(oxy-4,1-phenylene)-methylene]-bis-[A82846B]

Ex. #	G	G'	L	Name
17	A82846B	A82846B		1,5-pentanediyl-bis-[(oxy-3,1-phenylene]-methylene]-bis-[A82846B]
18	A82846B	A82846B		1,6-hexanediyl-bis-[(oxy-4,1-phenylene) methylene]-bis-[A82846B]
19	A82846B	A82846B		[3-methyl-1,5-pentanediyl] bis[(oxy 4,1-phenylene)-methylene]-bis-[A82846B]
20	A82846B	A82846B		1,7-heptanediyl-bis-[(oxy-4,1-phenylene)-methylene]-bis-[A82846B]
21	A82846B	A82846B		1,8-octanediyl-bis-[(oxy-4,1-phenylene)-methylene-bis[A82846B]
22	A82846B	A82846B	* HCl salt	* HCl salt
23	A82846B	A82846B		1,8-octanediyl-bis-[(oxy-3,1-phenylene)-methylene]-bis-[A82846B]
24	A82846B	A82846B		1,8-octanediyl-bis-[(oxy-3-n-pentyloxy-4,1-phenylene)methylene]--bis[A82846B]
25	A82846B	A82846B		1,9-nonanediyl-bis-[(oxy-4,1-phenylene]-methylene)-bis-[A82846B]

Ex. #	G	G'	L	Name
26	A82846B	A82846B		1,10-decanediyl-bis-[(oxy-4,1-phenylene)-methylene]-bis-[A82846B]
27	A82846B	A82846B		1,12-dodecanediyl-bis-[(oxy-4,1-phenylene)-methylene]-bis-[A82846B]
28	A82846B	A82846B		1,16-hexadecanediyl-bis-[(oxy-4,1-phenylene)-methylene]-bis-[A82846B]
29	A82846B	A82846B		1,2-ethanediyl-bis-[(oxy-1,2-ethyleneoxy-4,1-phenylene)methylene]--bis[A82846B]]
30	A82846B	A82846B		1,3-phenylene-bis-[(oxy-1,3-n-propyleneoxy-4,1-phenylene)methylene]--bis[A82846B]
31	A82846B	A82846B		1,4-phenylene-bis-[(carbonyloxy-1,2-ethyleneoxy-2,1-phenylene)methylene]-bis[A82846B]
32	A82846B	A82846B		1,3-[5-biphenylyl-bis-[(oxy-1,3-n-propyleneoxy-4,1-phenylene)methylene]-bis[A82846B]

Ex. #	G	G'	L	Name
49	A82846B	A82846B		1,6-hexanediylbis[oxy-[4,4'-biphenylene]-methylene]bis (A82846B)
50	A82846B	A82846B		1,3-phenylenebis[oxy-1,5-n-pentyleneoxy [4,1-phenylene]methylene] bis (A82846B)
51	A82846B	A82846B		1,8-octanediylbis[oxy-4-phenyl-[3,1-phenylene]-methylene]bis (A82846B)
53	Vanco	Vanco		1,8-octanediylbis-[(oxy-[3,1-phenylene)-methylene]-bis[vancomycin]
54	Vanco	Vanco		1,6-hexanediylbis[oxy-[4,4'-biphenylene]-methylene]-bis-[vancomycin]
55	Vanco	Vanco		1,8-octanediylbis-[(oxy-4-iodo-3,1-phenylene)methylene]bis-[vancomycin]

Ex. #	G	G'	L'	Name
56	Vanco	Vanco		1,8-octanediylbis-[(oxy-[4-phenyl-3,1-phenylene]-methylene]bis-[vancomycin]
57	Vanco	Vanco		1,3-phenylene-bis-[oxy-[5-methyl-5,1-hexylene]bis-[vancomycin]
58	Vanco	Vanco		1,4-butanediylbis-[oxy-[5-methyl-5,1-hexylene]-bis-[vancomycin]
59	Vanco	Vanco		1,12-dodecanediyl-bis-[(oxy-4,1-phenylene)-methylene]-bis-[vancomycin]
60	Vanco	Vanco		1,3-phenylene-bis-[(oxy-1,3-n-propyleneoxy-4,1-phenylene)methylene]-bis-[vancomycin].3HCl salt
61	Vanco	Vanco		5-n-pentyl-1,3-phenylene-bis[(oxy-1,3-n-propyleneoxy-4,1-phenylene)methylene]-bis-[vancomycin]

Ex. #	G	G'	L	Name
62	A82846B	A82846B		1,8-octanediylbis-[(oxy-4-iodo-3,1-phenylene)methylidene] bis [A82846B]
63	A82846B	A82846B		1,3-phenylene-bis-(oxy-5-methyl-5,1-hexylene)-bis[A82846B]
64	A82846B	A82846B		1,3-phenylene-bis-[(oxy-1,7-n-heptyleneoxy-4,1-phenylene)methylene]-bis-[A82846B]
65	A82846B	A82846B		1,4-butanediylbis-(oxy-5-methyl-5,1-hexylene]-bis-[A82846B]
66	A82846B	A82846B		1,3-phenylene-bis[(oxy-1,3-n-propyleneoxy-4,1-phenylene)methylene]-bis[A82846B]

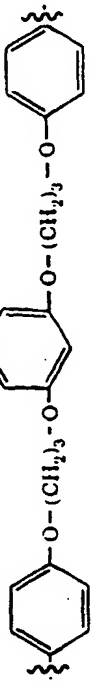
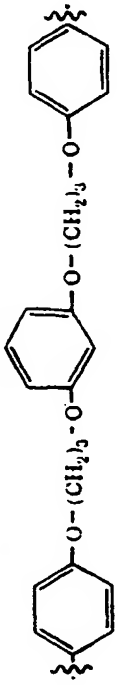
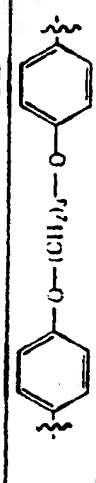
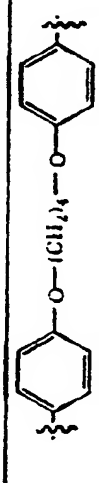
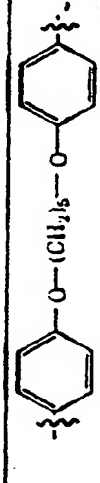
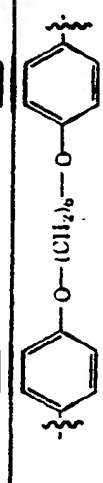
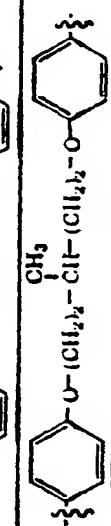
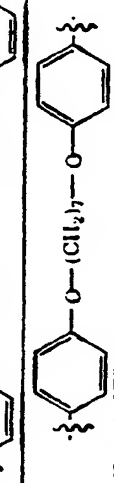
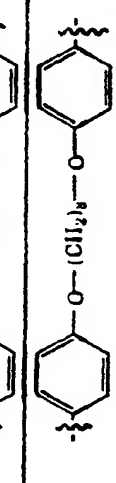
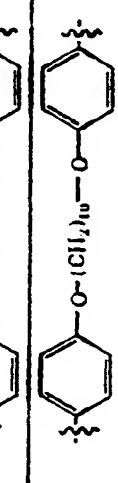
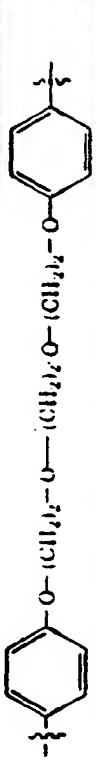
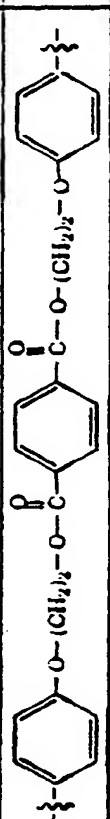
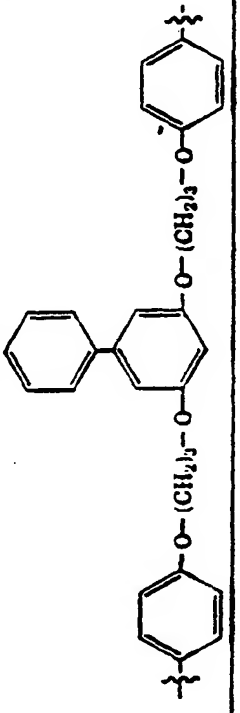
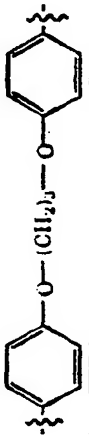
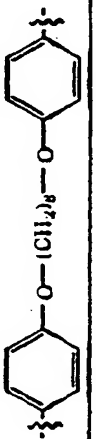
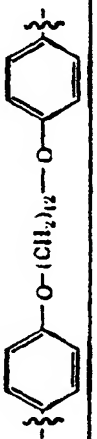
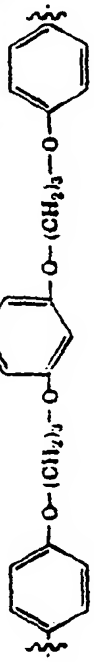
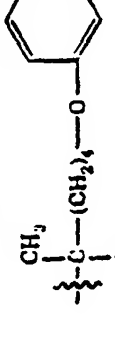
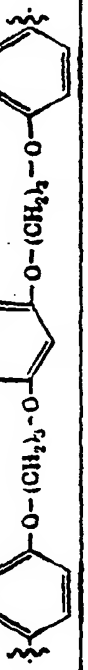
Ex. #	G	G'	L	Name
70	A82846B, (3-dimethyl amino propyl)-amide	A82846B		1,3-phenylenebis(oxy-1,3-n-propylene-oxy-4,1-phenylene)methylene] A82846B/A82846B,(3-dimethylaminopropyl)amide
71	A82846B, (3-dimethyl amino propyl)-amide	A82846B, (3-dimethyl amino propyl)-amide		1,3-phenylenebis(oxy-1,3-n-propylene-oxy-4,1-phenylene)methylene]bis-[A82846B,(3-dimethylaminopropyl)-amide]

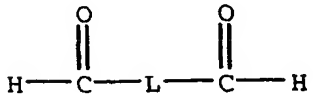
TABLE 2

Ex. #	G	L	Name
33	Vanco		N^4-(4-(2-(p-formylphenoxy)-ethoxy)benzyl)vancomycin
34	Vanco		N^4-(4-(3-(p-formylphenoxy)-n-propyloxy)benzyl)vancomycin
35	Vanco		N^4-(4-(4-(p-formylphenoxy)-n-butoxy)benzyl)vancomycin
36	Vanco		N^4-(4-(5-(p-formylphenoxy)-n-pentyloxy)benzyl)vancomycin
37	Vanco		N^4-(4-(6-(p-formylphenoxy)-n-hexyloxy)benzyl)vancomycin
38	Vanco		N^4-(4-(5-(p-formylphenoxy)-3-methyl-n-pentyloxy)benzyl)-vancomycin
39	Vanco		N^4-(4-(7-(p-formylphenoxy)-n-heptyloxy)benzyl)vancomycin
40	Vanco		N^4-(4-(8-(p-formylphenoxy)-n-octyloxy)benzyl)vancomycin
41	Vanco		N^4-(4-(10-(p-formylphenoxy)-n-decyloxy)benzyl)vancomycin

Ex. #	G	L	Name
42	Vanco		N^4-(4-(12-(p-formylphenoxy)-n-dodecyloxy)benzyl)vancomycin
43	Vanco		N^4-(4-(2-(2-(2-(p-formylphenoxy)ethoxy)ethoxy)ethoxy)benzyl)A82846B
44	Vanco		N^4-(4-(2-(4-(2-(p-formylphenoxy)ethoxycarbonyl)benzoyloxy)ethoxy)benzyl)vancomycin
45	Vanco		N^4-(4-(3-(3-(p-formylphenoxy)-n-propoxy)-5-phenylphenoxy)-n-propoxy)benzyl)vancomycin
46	A82846B		N^4-(4-(3-(p-formylphenoxy)-n-propyloxy)benzyl)A82846B
47	A82846B		N^4-(4-(8-(p-formylphenoxy)-n-octyloxy)benzyl)A82846B
48	A82846B		N^4-(4-(12-(p-formylphenoxy)-n-dodecyloxy)benzyl)A82846B

Ex. #	G	L	Name
52	Vanco		N^4-(4[3-(3-(p-formylphenoxy)-n-propyloxy)phenoxy)-n-propyloxy) benzyl)vancomycin
67	Vanco		N^4-(3-(8-(5-formyl-2-iodophenoxy)-n-octyloxy)-4-iodobenzyl)-vancomycin
68	Vanco		N^4-(6-(3-(5-formyl-5-methyl-n-hexyloxy)phenoxy)-2,2-dimethylhexyl)vancomycin
69	Vanco		N^4-(4-(3-(3-(p-formylphenoxy)-n-propyloxy)-5-n-pentylphenoxy)-n-propyloxyl-benzyl)-vancomycin

The compounds of the present invention are prepared by reacting vancomycin or A82846B with a bisaldehyde of the formula:



III

to form an intermediate Schiff base, which is subsequently reduced to obtain the compounds of Formula I and II.

Many of the bisaldehydes to be employed as starting materials are known compounds. All of them can be prepared by techniques known to those skilled in the art, per various references;

J. Org. Chem., **26**, 474, (1961)
J. Het. Chem., **27**, 1007 (1990)
J.A.C.S., **73**, 1872 (1951)
J.A.C.S., **109**, 2260 (1987)
J. Chem. Soc. Perkin I, 189 (1983)
Syn. Comm., **18(12)**, 1379 (1988)
Chem. Letters, 587 (1995)
Macromolecules, 6045 (1992);
J. Chem. Soc. Chem. Comm. 1463 (1991)
J. Polym. Sci. Part A, Polymer Chem. 31(12) 2899 (1993)
J. Chem. Res. Synop. (8), 296 (1994)
Farmco Ed. Sci. 15, 468 (1960)
Makromol. Chem. 191 (4) 815 (1990)
J. Polym. Sci. Part A, Polymer Chem. 29(3) 361 (1991)
Makromol. Chem. 65, 54 (1963)

The reaction of bisaldehyde with vancomycin or A82846B is carried out in accordance with prior art condensations of amine and aldehyde to form Schiff bases, and their subsequent reduction.

Thus, the present condensation is typically conducted in a polar solvent, such as dimethylformamide or methanol, or a mixture of polar solvents. The reaction goes forward over a range of temperatures, such as from 25°C to 100°C, but is preferably conducted at temperatures of about 60°C to 70°C. The reaction is preferably conducted under an inert atmosphere, such as nitrogen or argon.

The reaction yields a Schiff base of the formula

G=CH-L-CH=G'

where both aldehyde groups have reacted with glycopeptide, or of the formula

G=CH-L-CHO

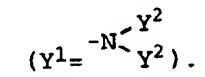
where only one aldehyde group has reacted with glycopeptide.

The Schiff base is subsequently reduced. Preferably, the reduction is conducted in the same reaction mixture in a polar solvent, and employing a chemical reducing agent. Metal borohydrides, such as sodium borohydride and sodium cyanoborohydride are preferred. The reaction goes forward over a range of temperatures, such as from about 25°C to about 100°C; preferably, the reaction is conducted at about 60°C to 70°C.

Depending somewhat on concentration of reagents, the condensation of bisaldehyde with vancomycin or A82846B and subsequent reduction will yield a dimer of Formula I, a monosubstituted derivative of Formula II, or a mixture of both. Generally, both products are produced. However, some control of the products can be achieved by the amount of reactants employed. A dimer of Formula I requires two molecular proportions of vancomycin or A82846B per molecular proportion of bisaldehyde, whereas a compound of Formula II requires equimolar amounts of the reactants. Preferably the reaction is continued through the reduction, and the respective products separated at that time.

The product, or mixture of products, can be isolated and purified if desired in a conventional manner, such as by HPLC. Characterization of products is best accomplished by Fast Atom Bombardment Mass Spectroscopy (FABMS).

In addition to the foregoing synthetic route, compounds of the present invention can be prepared in an alternate route. In this alternate route, a dimer is prepared by the foregoing synthetic route, and further changes to the structure of the glycopeptide are made subsequently. This approach to synthesizing the present dimers is illustrated by Preparations 7 and 8 below in which a dimer of the present invention is reacted with an amine to convert the acid of the glycopeptide to an amide



Other modifications of the glycopeptide portion of a dimer can likewise be made. Techniques for such modifications are known to those skilled in the art; see Glycoceptide Antibiotics, edited by Ramakrishnan Nagarajan (Marcel Dekker, Inc., New York, 1994), and references cited therein. This volume is incorporated herein by reference.

When it is desired to employ a salt, a compound of the present invention can be reacted with a mineral or organic acid or an inorganic base, in techniques well known to those skilled in the art. Pharmaceutically-acceptable salts are preferred.

The following examples report preparations of illustrative compounds of the present invention.

The HPLC procedures reported in these examples were as follows:

Analytical ("Conditions A"): Reactions were monitored by analytical HPLC using a Waters μBondapak C_{18} column (3.9x300 mm) and UV detection at 280 nm. Elution was accomplished with a linear gradient of 5% CH_3CN - 95% buffer to 80% CH_3CN - 20% buffer over 30 minutes. The buffer used was 0.5% triethylamine in water, adjusted to pH 3 with H_3PO_4.

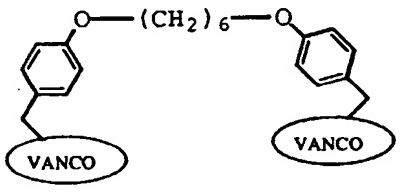
Preparative ("Conditions B"): Crude reaction mixtures were purified by preparative HPLC using a Waters C_{18} Nova-Pak column (40x300 mm) and UV detection at 280 nm. Elution was accomplished with a linear gradient of 5% CH_3CN - 95% buffer to 80% CH_3CN - 20% buffer over 30 minutes. The buffer used was 0.5% triethylamine in water, adjusted to pH 3 with H_3PO_4. The desired fractions were subsequently desalted with a Waters C_{18} Sep-Pak (35 cc) followed by lyophilization. Alternatively, a buffer containing 0.1% TFA in H_2O can be used, in which case the TFA salt is obtained directly after lyophilization.

Compounds were desalted as follows. A Waters Sep-Pak cartridge was pre-wet with methanol (2-3 column volumes) then conditioned with water (2-3 column volumes). The sample, dissolved in a minimum volume of water, was loaded onto the Sep-Pak column which was then washed with water (2-3 column volumes) to remove the unwanted salts. The product was then eluted with an appropriate solvent system, typically 1:1 CH_3CN/H_2O, CH_3CN, and/or methanol. The organic solvent component was removed *in vacuo* and the resulting aqueous solution lyophilized to give the final product.

Preparation 1:

Synthesis of Example 5, 1,6-hexanediylbis[(oxy-4,1- phenylene)methylene]bis[vancomycin]

(one-pot synthesis of vancomycin dimer)



A dry 100 mL round bottom flask was charged with vancomycin•HCl (250 mg, 0.168 mmol.), and 1,6-bis(4'-formylphenoxy)-n-hexane (101 mg, 0.310 mmol.). Anhydrous DMF (6 mL) was added to the flask and the resulting mixture was stirred under N_2 and heated to 70°C. After 3.5 hours, sodium cyanoborohydride (80 mg, 1.3 mmol.) was added in one portion, and the reaction mixture was maintained at 70°C for one additional hour. The reaction mixture was cooled, and stored at 0°C overnight.

The reaction mixture was then concentrated in vacuo to give a residue which was re-dissolved in 1:1 H_2O:CH_3CN (5 mL) and HOAc (0.5 mL). The resulting solution was purified by preparatory HPLC (conditions B). The desired frac-

tions, as determined by analytical HPLC (conditions A), were concentrated in vacuo to ~ 1.5 mL, and desalted. After lyophilization, 1,6-hexanediylbis[(oxy-4,1-phenylene)methylene]bis [vancomycin] was obtained (24.3 mg, 0.008 mmol., 10.0 % yield) as a white powder.

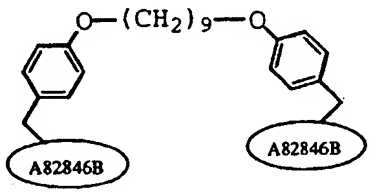
HPLC (conditions A) retention time: 13.6 min.

FABMS shows peak of (M+6H) at 3195.

Preparation 2:

Synthesis of Example 25, 1,9-nonanediylbis[(oxy-4,1-phenylene)methylene]bis[A82846B]

(one-pot synthesis of A82846 dimer)



A dry 100 mL round bottom flask was charged with A82846B·tri-acetate salt (278 mg, 0.157 mmol.), and 1,9-bis-(4'-formylphenoxy)-n-nonane (103.7 mg, 0.282 mmol.). Anhydrous DMF (15 mL) and anhydrous MeOH (15 mL) were added to the flask and the resulting mixture was stirred under N_2 and heated to 70°C. After 3.5 hours, sodium cyanoborohydride (68 mg, 1.08 mmol.) was added in one portion, and the reaction mixture was maintained at 70°C for one additional hour.

The reaction mixture was then concentrated in vacuo to give a residue which was re-dissolved in 1:1 H_2O:CH_3CN (5 mL) and HOAc (0.5 mL). The resulting solution was purified by preparatory HPLC (conditions B). The desired fractions, as determined by analytical HPLC (conditions A), were concentrated in vacuo to ~ 1.5 mL, and desalted. After lyophilization, 1,9-nonanediylbis[(oxy-4,1-phenylene)methylene]bis[epivancomycin] was obtained (25.7 mg, 0.007 mmol., 9.3 % yield) as a white powder.

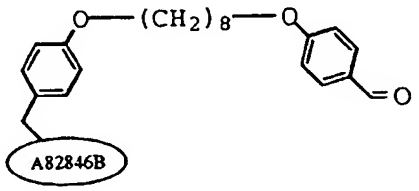
HPLC (conditions A) retention time: 14.9 min.

FABMS shows peak of (M+5H)at 3522.

Preparation 3:

Synthesis of Example 47, N^4-(4-(8-(p-formylphenoxy)-n-octyloxy)benzyl)A82846B

(synthesis of Formula II)



A dry 100 mL round bottom flask was charged with A82846B·tri-acetate salt (278 mg, 0.157 mmol.), and 1,8-bis-(4'-formylphenoxy)-n-octane (100 mg, 0.19mmol.). Anhydrous DMF (15 mL) and anhydrous MeOH (15 mL) were added to the flask and the resulting mixture was stirred under N_2 and heated to 70 °C. After 3.5 hours, sodium cyanoborohydride (48 mg, 0.739mmol.) was added in one portion, and the reaction mixture was maintained at 70 °C for one additional hour.

The reaction mixture was then concentrated in vacuo to give a residue which was re-dissolved in 1:1 H_2O:CH_3CN (5 mL) and HOAc (0.5 mL). The resulting solution was purified by preparatory HPLC (conditions B). The desired fractions, as determined by analytical HPLC (conditions A), were concentrated in vacuo to ~ 1.5 mL, and desalted. After lyophilization, N^4-(4-(8-(p-formylphenoxy)-n-octyloxy)benzyl)A82846B was obtained (26.3mg, 0.013 mmol., 8.6%

yield) as a white powder.

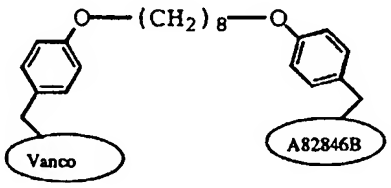
HPLC (conditions A) retention time: 19.9 min.

FABMS shows peak of (M+ 2H) at 1930.

Preparation 4:

Synthesis of Example 13, 1,8-octanediylbis((oxy-4,1-phenylene)methylene][vancomycin][A82846B]

(synthesis of hybrid dimer)



A dry round bottom flask was charged with vancomycin•HCl (75 mg, 0.052 mmol.), and N^4-(4-(8-(p-formylphenoxy)-n-octyloxy)benzyl)A82846B (50 mg, 0.026 mmol.). Anhydrous DMF (6 mL) was added to the flask and the resulting mixture was stirred under N_2 and heated to 70°C. After 5 hours, sodium cyanoborohydride (59 mg, 0.93 mmol.) was added in one portion, and the reaction mixture was maintained at 70°C for one additional hour. The reaction mixture was cooled, and stored at 0°C overnight.

The reaction mixture was then concentrated in vacuo to give a residue which was re-dissolved in 1:1 H_20:CH_3CN (5 mL) and HOAc (0.5 mL). The resulting solution was purified by preparatory HPLC (conditions B). The desired fractions, as determined by analytical HPLC (conditions A), were concentrated in vacuo to ~ 1.5 mL, and desalted. After lyophilization, 1,8-octanediylbis[(oxy-4,1-phenylene)methylene][vancomycin] [A82846B] was obtained (5.2 mg, 0.002 mmol., 7.6 % yield) as a white powder.

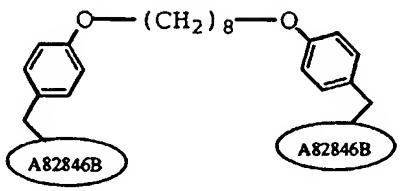
HPLC (conditions A) retention time: 14.5 min.

FABMS shows peak of (M+6H) at 3364.

Preparations 5 & 6:

Synthesis of Example 47, N^4-(4-(8-(p-formylphenoxy)-n-octyloxy)benzyl)A82846B, and Example 21, 1,8-octanediylbis [(oxy-4,1-phenylene)methylene]bis[A82846B]

(two-step synthesis of A82846 dimer)



A dry flask was charged with A82846B·tri-acetate salt (5.0 g, 0.003 mol.), and 1,8-bis(4'-formylphenoxy)-n-octane (1.93 g, 0.006 mol.). Anhydrous DMF (300 mL) and anhydrous MeOH (300 mL) were added to the flask and the resulting mixture was stirred under N_2 and heated to 70°C. After 3.75 hours, sodium cyanoborohydride (0.76 g, 0.012 mol.) was added in one portion, and the reaction mixture was maintained at 70°C for one additional hour. The reaction was cooled and stored at 0°C overnight.

The reaction mixture was then concentrated in vacuo to give a residue which was re-dissolved in 1:1 H_20:CH_3CN (200 mL) and HOAc (5 mL). The resulting solution was purified by preparatory HPLC (conditions B). The desired fractions, as determined by analytical HPLC (conditions A), were concentrated in vacuo to ~ 1.5 mL, and desalted. After lyophilization, N^4-(4-(8-(p-formylphenoxy)-n-octyloxy)benzyl)A82846B was obtained (387.4 mg, 0.2 mmol., 6.6 % yield) as a white powder.

HPLC (conditions A) retention time: 19.9 min.

FABMS shows peak of (M+3H)at 1932.

A dry flask was charged with N^4-(4-(8-(p-formylphenoxy)-n-octyloxy)benzyl)A82846B (20.0 mg, 0.01 mmol), and A82846B (32.9 mg, 0.021 mmol). Anhydrous DMF (3 mL) and anhydrous MeOH (3 mL) were added to the flask and the resulting mixture was stirred under N_2 and heated to 70°C. After 2 hours, sodium cyanoborohydride (5.0 mg, 0.079 mmol) was added in one portion, and the reaction mixture stirred an additional 0.25 hours.

The reaction mixture was then concentrated in vacuo to give a residue which was redissolved in 1:1 H_2O:CH_3CN (5 mL). The resulting solution was purified by preparatory HPLC (conditions D). The desired fraction, as determined by analytical HPLC (conditions A), were concentrated in vacuo to ~1.5 mL, and desalted. After lyophilization, 1,8-octanediylbis[(oxy-4,1-phenylene)methylene]bis[A82846B] was obtained (3.0 mg, 0.001 mmol, 8.6 % yield) as a white powder.

HPLC (conditions A) retention time: 13.6 min.

FABMS shows peak of (M+5H) at 3508.

Preparations 7 & 8:

Synthesis of Example 70, 1,3-phenylenebis[oxy-1,3-n-propylene-oxy-4,1-phenylene)methylene]A82846B/A82846B, (3-dimethylaminopropyl)amide, and Example 71, 1,3-phenylenebis[oxy-1,3-n-propylene-oxy-4,1-phenylene) methylene]bis[A82846B, (3-dimethylaminopropyl)amide]

A dry round bottom flask was charged with 1,3-phenylene-bis-[(oxy-1,3-n-propyleneoxy-4,1-phenylene)methylene]-bis[A82846B] (50.0 mg, 0.014 mmol) and 1 mL DMSO. PyBOP (14.5 mg, 0.028 mmol) and 3-dimethylaminopropylamine (2.8 mg, 0.028 mmol) were added and the reaction was stirred at room temperature under nitrogen for one hour. The reaction mixture was then concentrated in vacuo to give a residue which was re-dissolved in 1:1 H_2O:CH_3CN (5 mL). The resulting solution was purified by preparatory HPLC (conditions B). The desired fractions, as determined by analytical HPLC (conditions A) were concentrated in vacuo to ~ 1.5 mL, and desalted as in previous examples. After lyopholization 1,3-phenylenebis[oxy-1,3-n-propylene-oxy-4,1-phenylene)methylene]bis[A82846B,(3-dimethylaminopropyl)amide] (6.9 mg, 13.1% yield) and 1,3-phenylenebis[oxy-1,3-n-propylene-oxy-4,1-phenylene) -methylene] A82846B/A82846B,(3-dimethylaminopropyl)amide (6.6 mg, 12.8% yield) were obtained as white powders.

1,3-phenylenebis[oxy-l,3-n-propylene-oxy-4,1-phenylene)methylene]bis[A82846B, (3-dimethylaminopropyl)-amide]

HPLC (conditions A) retention time: 13.2 min.

FABMS shows peak of (M+9H) at 3761.

1,3-phenylenebis[oxy-1,3-n-propylene-oxy-4,1-phenylene)-methylene]A828468/A82846B, (3-dimethylaminopropyl)amide

HPLC (conditions A) retention time: 13.7 min.

FABMS shows peak of (M+6H) at 3674.

Details concerning the synthesis of all of the compounds of TABLES 1 and 2, as well as identifying characteristics on the same compounds, are presented in TABLES 3 and 4.

TABLE 3

Ex. #	Aldehyde	HPLC * Retention Minutes	% yield	FAB•MS M/Z	M+x H
1	1,2-bis(4-formylphenoxy)-n-ethane	11.5	1.86	3136	3
2	1,4-bis(2-formylphenoxy)-n-butane	11.8	0.79	3165	4
3	1,5-bis(4-formylphenoxy)-n-pentane	12.9	5.42	3178	4
4	1,5-bis(3-formylphenoxy)-n-pentane	13.0	4.08	3179	4
5	1,6-bis(4-formylphenoxy)-n-hexane	13.6	9.05	3195	6
6	3-methyl-1,5-bis(4-formylphenoxy)-n-pentane	13.5	4.54	3193	4
7	1,7-bis(4-formylphenoxy)-n-heptane	14.7	5.00	3207	5
8	1,8-bis(4-formylphenoxy)-n-octane	15.5	3.91	3219	2
9	1,9-bis(4-formylphenoxy)-n-nonane	16.4	4.41	3235	4
10	1,2-bis(2-(4-formylphenoxy)-ethoxy)ethane	12.3	1.89	3226	4
11	1,4-bis(2-(p-formylphenoxy)-ethoxy)carbonyl-benzene	13.0	10.50	3331	6
12	1,3-bis(3-(p-formylphenoxy)-n-propyloxy)-benzene	15.5	3.10	3300	4
13	1,8-bis(4-formylphenoxy)-n-octane	14.5	5.95	3364	4
14	1,3-bis(4-formylphenoxy)-propane	9.4	14.29	3436	4
15	1,4-bis(2-formylphenoxy)-n-butane	10.2	5.91	3452	5

Ex. #	Aldehyde	HPLC * Retention Minutes	% yield	FAB•MS M/Z	M+x H
16	1,5-bis(4-formylphenoxy)-n-pentane	10.4	3.86	3466	5
17	1,5-bis(3-formylphenoxy)-n-pentane	11.3	22.41	3465	4
18	1,6-bis(4-formylphenoxy)-n-hexane	11.3	5.46	3478	4
19	3-methyl-1,5-bis(4-formylphenoxy)-n-pentane	11.3	8.14	3479	4
20	1,7-bis(4-formylphenoxy)-n-heptane	12.5	5.73	3494	5
21	1,8-bis(4-formylphenoxy)-n-octane	14.0	13.31	3508	5
23	1,8-bis(3-formylphenoxy)-n-octane	14.4	21.23	3508	5
24	1,8-bis(4-formyl-2-n-pentyloxy-phenoxy)-n-octane	20.8	16.91	3680	5
25	1,9-bis(4-formylphenoxy)-n-nonane	14.9	9.31	3522	5
26	1,10-bis(4-formylphenoxy)-n-decane	15.9	8.87	3535	5
27	1,12-bis(4-formylphenoxy)-n-dodecane	17.7	1.32	3565	6
28	1,16-bis(4-formylphenoxy)-n-hexadecane	20.4	4.05	3625	9
29	1,2-bis(2-(4-formylphenoxy)-ethoxy)ethane	10.2	6.28	3511	4
30	1,3-bis(3-(p-formylphenoxy)-n-propyloxy)-benzene	15.2	22.96	3589	5
31	1,4-bis(2-(p-formylphenoxy)-ethoxy)carbonyl-benzene	11.7	24.94	3615	5

Ex. #	Aldehyde	HPLC * Retention Minutes	% yield	FAB•MS M/Z	M+x H
32	5-phenyl-1,3-bis(3-(p-formylphenoxy)-n-propyloxy)-benzene	16.8	12.88	3664	5
49	1,6-bis(4-(4-formylphenyl)-phenoxy)hexane	16.2	11.58	3633	5
50	1,3-bis(5-(4-formylphenoxy)-n-pentyloxy)-benzene	17.0	9.31	3645	6
51	1,8-bis(2-phenyl-5-formylphenoxy)-octane	18.3	10.83	3662	6
53	1,8-bis(3-formylphenoxy)-n-hexane	15.3	2.1	3221	4
54	1,6-bis(4-(4'-formylphenoxy)-phenoxy)-n-hexane	18.2	6.1	3347	6
55	1,8-bis(3-formyl-2-iodophenoxy)-n-hexane	22.9	2.2	3471	3
56	1,8-bis(2-phenyl-5-formylphenoxy)-n-octane	19.3	2.8	3374	4
57	1,3-bis(6-(2-dimethyl)-1-hexanaloxy)-benzene	15.5	8.2	3229	4
58	1,4-bis(6-(2-dimethyl)-1-hexanaloxy)-butane	13.5	6.1	3209	4
59	1,12-bis(4-formylphenoxy)-n-dodecane	21.6	6.8	3278	5
60	1,3-bis(3-(p-formylphenoxy-n-propyloxy)-benzene	HCL SALT			
61	1,3-bis(3-(p-formylphenoxy-n-propyloxy)-5-n-pentylbenzene	36.6	12.7	3660	8
62	1,8-bis(3-formyl-2-iodophenoxy)-n-octane	17.1	5.4	3762	6

Ex. #	Aldehyde	HPLC * Retention Minutes	% yield	FAB•MS M/Z	M+x H
63	1,3-bis(6-(2-dimethyl)-1-hexanaloxy)-benzene	13.3	15.5	3516	5
64	1,3-bis(3-(p-formylphenoxy-n-heptyloxy)-benzene	19.3	1.4	3701	6
65	1,4-bis(6-(2-dimethyl)-1-hexanaloxy)-butane	13.5	24.8	3495	4
66	1,3-bis(3-(p-formylphenoxy-n-propyloxy)-benzene	HCL SALT			
70	1,3-bis(3-(p-formylphenoxy)-n-propyloxy)-benzene	13.7	12.8	3674	6
71	1,3-bis(3-(p-formylphenoxy)-n-propyloxy)-benzene	13.2	13.1	3761	9

* Conditions A

TABLE 4

Ex. #	Aldehyde	HPLC * Retention, Minutes	% Yield	FAB•MS M/Z	M+ xH
33	1,2-bis(4-formylphenoxy)-n-ethane	13.1	2.58	1706	5
34	1,2-bis(4-formylphenoxy)-n-propane	15.2	13.08	1718	0
35	1,2-bis(4-formylphenoxy)-n-butane	14.7	8.12	1734	4
36	1,2-bis(4-formylphenoxy)-n-pentane	17.1	21.89	1746	4
37	1,2-bis(4-formylphenoxy)-n-hexane	18.0	8.37	1760	2
38	1,2-bis(4-formylphenoxy)-3-methyl-n-pentane	17.7	5.81	1760	1
39	1,2-bis(4-formylphenoxy)-n-heptane	19.0	27.99	1774	2
40	1,2-bis(4-formylphenoxy)-n-octane	18.5	11.89	1789	3
41	1,2-bis(4-formylphenoxy)-n-decane	21.7	0.85	1816	4

* Conditions A

TABLE 4 (continued)

Ex. #	Aldehyde	HPLC * Retention, Minutes	% Yield	FAB•MS M/Z	M+ xH
42	1,2-bis(4-formylphenoxy)-n-dodecane	23.4	12.53	1841	1
43	1,2-bis(2-(4-formylphenoxy) ethoxyethane	14.4	5.57	1794	4
44	1,2-bis(2-(4-formylphenoxy) ethoxy-benzoate	16.5	5.64	1897	3
45	1,2-bis(2-(4-formylphenoxy)-propyloxy)-5-phenylbenzene	21.0	4.96	1946	5
46	1,3-bis(4-formylphenoxy)-propane	15.2	4.90	1861	2
47	1,3-bis(4-formylphenoxy)-octane	19.9	8.69	1930	1
48	1,3-bis(4-formylphenoxy)-dodecane	23.3	1.19	1984	1
52	1,3-bis(3-(p-formylphenoxy)-n-propyloxy)-benzene	18.8	3.10	1871	5
67	1,8-bis(3-formyl-2-iodophenoxy)-n-octane	21.3	4.5	2042	5
68	1,3-bis(6-(2-dimethyl)-1-hexanaloxy)-benzene	18.3	13.2	1798	4
69	1,3-bis(3-(p-formylphenoxy-n-propyloxy)-5-n-pentylbenzene	22.4	3	1940	5

* Conditions A

The compounds of Formulae I and II are useful for the treatment of bacterial infections. Therefore, in another embodiment, the present invention is directed to a method for controlling a bacterial infection in a host animal, typically a warm-blooded animal, which comprises administering to the host animal an effective, antibacterial amount of a compound of Formula I or II. In this embodiment, the compounds of the present invention can be used to control and treat infections due to various bacteria, but especially gram-positive bacteria. In a preferred embodiment, the compounds are used to control and treat infections due to bacteria resistant to existing antibacterials. For example, certain bacteria are resistant to methicillin, and yet others are resistant to vancomycin and/or teicoplanin. The present compounds provide a technique for controlling and treating infections due to such resistant bacterial species.

In carrying out this embodiment of the invention, the compounds can be administered by any of the conventional techniques, including the oral route and parenteral routes such as intravenous and intramuscular. The amount of compound to be employed is not critical and will vary depending on the particular compound employed, the route of administration, the severity of the infection, the interval between dosings, and other factors known to those skilled in the art. In general, a dose of from about 0.5 to about 100 mg/kg will be effective; and in many situations, lesser doses of from about 0.5 to about 50 mg/kg will be effective. A compound of the present invention can be administered in a single dose, but in the known manner of antibacterial therapy, a compound of the present invention is typically administered repeatedly over a period of time, such as a matter of days or weeks, to ensure control of the bacterial infection.

Also in accordance with known antibacterial therapy, a compound of the present invention is typically formulated for convenient delivery of the requisite dose. Therefore, in another embodiment, the present invention is directed to a pharmaceutical formulation comprising a compound of either Formula I or II, in combination with a pharmaceutically-acceptable carrier. Such carriers are well known for both oral and parenteral routes of delivery. In general, a formulation will comprise a compound of the present invention in a concentration of from about 0.1 to about 90% by weight, and often from about 1.0 to about 3%.

The antibacterial efficacy of the present compounds is illustrated by following TABLES 5 and 6. The minimal inhibitory concentrations (MICs) were determined using a standard broth micro-dilution assay. TABLE 6 presents a comparison of the activity of illustrative compounds against representative vancomycin-resistant and vancomycin-sensitive enterococci (Enterococcus faecium and Enterococcus faecalis, mean geometric MIC (mcg/mL), as determined by the standard broth micro-dilution assay.

TABLE 5

In Vitro Antimicrobial Activity									
	MIC (mcg/ml) / Compound								
Organism	Vancomycin	A82846B	1	2	3	4	5	6	7
Staphylococcus aureus 446	0.5	0.25	4	16	8	8	4	4	2
Staphylococcus aureus 489	0.125	≤0.06	0.5	0.5	0.5	2	0.5	0.25	0.5
Staphylococcus aureus 447	0.5	0.25	16	>64	32	32	16	H	8
Staphylococcus aureus X400	0.5	0.125	1	1	2	2	1	1	1
Staphylococcus aureus X778	0.5	0.125	1	4	2	4	1	1	1
Staphylococcus aureus 491	1	0.25	0.5	0.5	0.25	2	0.25	0.5	0.5
Staphylococcus aureus S13E	0.5	0.125	2	2	2	4	1	2	0.5
Staphylococcus aureus SA1199	0.5	0.125	4	4	32	4	2	4	1
Staphylococcus aureus SA1199A	0.125	≤0.06	0.5	0.125	0.5	1	0.25	0.5	0.25
Staphylococcus aureus SA1199B	0.5	0.125	4	4	16	4	2	4	1
Staphylococcus haemolyticus 105	16	1	8	4	8	8	4	8	2
Staphylococcus haemolyticus 415	8	4	16	>64	16	16	8	8	8
Staphylococcus epidermidis 270	16	0.25	8	>64	16	16	4	4	4
Enterococcus faecium 180	>64	8	0.25	1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Enterococcus faecium 180-1	0.5	0.125	0.5	1	0.5	1	0.25	≤0.06	≤0.06
Enterococcus faecalis 2041	2	0.25	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.5
Enterococcus faecalis 276	1	0.125	0.25	0.25	0.5	0.25	0.5	0.5	1
Enterococcus gallinarum 245	4	0.25	0.06	0.06	0.06	0.06	0.06	0.06	0.06
Haemophilus influenzae RD	>64	>64		>64		>64			
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	0.5		0.06	0.06	0.06	0.06	0.06	0.06	0.06
Streptococcus pneumoniae P1	0.25		0.06	0.06	0.06	0.06	0.06	0.06	0.06

TABLE 5

Organism	8	9	10	11	12	13	14	15	16
Staphylococcus aureus 446	8	1	8	16	8	8	4	4	8
Staphylococcus aureus 489	4	1	4	4	2	2	1	0.25	2
Staphylococcus aureus 447	32	4	16	64	8	16	16	64	>64
Staphylococcus aureus X400	4	1	4	8	2	4	2	0.5	2
Staphylococcus aureus X778	4	1	4	16	2	2	1	0.5	2
Staphylococcus aureus 491	2	0.5	1	0.25	2	1	0.25	0.125	0.5
Staphylococcus aureus S13E	8	2	4	8	4	4	2	1	1
Staphylococcus aureus SA1199	16	1	4	16	4	4	4	1	4
Staphylococcus aureus SA1199A	2	0.25	1	1	1	0.5	0.125	≤0.06	0.5
Staphylococcus aureus SA1199B	8	0.5	4	32	4	4	2	4	2
Staphylococcus haemolyticus 109	8	0.5	4	64	4	1	4	8	1
Staphylococcus haemolyticus 419	8	4	16	64	4	8	16	>64	32
Staphylococcus epidermidis 270	8	2	16	32	4	8	8	64	32
Enterococcus faecium 180	0.125	≤0.06	4	2	≤0.06	0.125	0.25	0.25	0.125
Enterococcus faecium 180-1	0.5	0.25	1	0.25		0.5	≤0.06	0.25	0.5
Enterococcus faecalis 2041	0.25	0.5	0.25	≤0.06	0.25	0.25	0.25	0.125	0.25
Enterococcus faecalis 276	2	1	1	0.5	1	1	0.5	0.5	1
Enterococcus gallinarum 245	0.25	0.06	0.125	0.06	0.06	0.06	0.06	0.06	0.25
Haemophilus influenzae RD	>64	>64	64			>64	>64		>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	8	0.06	0.06	0.06	0.06	0.06	0.06	0.06	1
Streptococcus pneumoniae P1	4	0.06	0.06	0.06	0.06	0.06	0.06	0.125	1

TABLE 5

Organism	17	18	19	20	21	22	23	24	25
Staphylococcus aureus 446	4	8	4	4	8	4	2	2	4
Staphylococcus aureus 489	1	4	0.25	2	2	4	1	2	4
Staphylococcus aureus 447	>64	64	32	64	64	32	8	16	64
Staphylococcus aureus X400	1	2	0.5	2	2	4	1	2	2
Staphylococcus aureus X778	2	2	0.5	1	1	1	0.25	2	2
Staphylococcus aureus 491	0.5	0.25	0.25	1	2	2	1	1	2
Staphylococcus aureus S13E	1	2	1	2	1	2	4	2	4
Staphylococcus aureus SA1199	1	2	1	4	1	2	2	2	4
Staphylococcus aureus SA1199A	0.125	0.25	0.125	0.25	0.25	0.5	0.5	1	0.5
Staphylococcus aureus SA1199B	1	1	2	2	1	4	1	2	4
Staphylococcus haemolyticus 105	0.5	0.5	8	2	16	4	4	2	2
Staphylococcus haemolyticus 419	8	16	32	32	8	16	4	4	16
Staphylococcus epidermidis 270	64	16	16	16	8	8	4	4	16
Enterococcus faecium 180	0.125	≤0.06	0.125	≤0.06	0.125	0.25	0.125	1	0.25
Enterococcus faecium 180-1	0.125	0.25	1	1	0.5	0.5		0.5	1
Enterococcus faecalis 2041	0.125	0.25	0.25	≤0.06	0.5	0.5	0.5	1	1
Enterococcus faecalis 276	0.125	0.125	1	0.25	1	1	1	2	1
Enterococcus gallinarum 245	0.06	0.06	0.06	0.06	0.06	0.06	0.125	0.5	0.25
Haemophilus influenzae RD	>64	>64		>64	>64	>64		>64	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.25	0.25
Streptococcus pneumoniae P1	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.125

TABLE 5

Organism	26	27	28	29	30	31	32	33	34
Staphylococcus aureus 446	4	16	>64	16	1	1	16	0.25	≤0.06
Staphylococcus aureus 489	2	8	64	1	1	1	4	≤0.06	≤0.06
Staphylococcus aureus 447	>64	>64	>64	64	4	8	>64	0.5	≤0.06
Staphylococcus aureus X400	1	16	32	1	1	0.5	4	≤0.06	≤0.06
Staphylococcus aureus X778	2	8	32	2	0.5	0.25	2	0.125	≤0.06
Staphylococcus aureus 491	2	8	16	≤0.06	0.25	≤0.06	2	≤0.06	≤0.06
Staphylococcus aureus S13E	2	8	64	4	0.5	0.25	8	0.125	≤0.06
Staphylococcus aureus SA1199	2	8	64	2	1	0.5	8	0.25	≤0.06
Staphylococcus aureus SA1199A	1	4	16	0.5	≤0.06	≤0.06	2	<0.06	≤0.06
Staphylococcus aureus SA1199B	2	8	64	4	1	0.5	8	0.125	≤0.06
Staphylococcus haemolyticus 105	4	32	32	0.25	0.25	0.25	4	1	0.5
Staphylococcus haemolyticus 415	16	64	64	>64	4	16	8	8	2
Staphylococcus epidermidis 270	8	32	64	32	1	2	16	0.5	0.25
Enterococcus faecium 180	0.5	1	8	0.25	0.125	1	1	16	0.5
Enterococcus faecium 180-1	1	1	8	0.5	0.125	≤0.06	2	0.125	≤0.06
Enterococcus faecalis 2041	1	4	8	0.125	0.25	≤0.06	2	0.25	≤0.06
Enterococcus faecalis 276	2	4	8	0.25	0.5	0.125	2	0.125	≤0.06
Enterococcus gallinarum 245	1	2	4	0.06	0.125	0.06	1	2	1
Haemophilus influenzae RD	>64	>64	>64			>64	>64		
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	4	0.5	64	0.06	0.06	0.06	0.5	0.06	0.06
Streptococcus pneumoniae P1	2	1	64	0.06	0.06	0.06	0.125	0.06	0.06

TABLE 5

Organism	35	36	37	38	39	40	41	42	43
Staphylococcus aureus 446	≤0.06	≤0.06	0.25	0.125	≤0.06	0.5	4	2	2
Staphylococcus aureus 489	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.125	2	2	1
Staphylococcus aureus 447	≤0.06	≤0.06	0.125	≤0.06	1	0.25	8	4	4
Staphylococcus aureus X400	≤0.06	≤0.06	≤0.06	≤0.06	0.5	0.125	4	2	2
Staphylococcus aureus X778	≤0.06	≤0.06	≤0.06	0.125	0.5	≤0.06	2	1	2
Staphylococcus aureus 491	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	2	2	0.5
Staphylococcus aureus S13E	≤0.06	≤0.06	≤0.06	≤0.06	0.5	0.25	4	4	2
Staphylococcus aureus SA1199	≤0.06	≤0.06	≤0.06	≤0.06	0.25	0.25	4	2	2
Staphylococcus aureus SA1199A	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.25	1	0.5
Staphylococcus aureus SA1199B	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	1	8	4	4
Staphylococcus haemolyticus 105	0.25	0.25	1	0.5	0.125	1	1	2	1
Staphylococcus haemolyticus 415	4	2	2	2	0.5	4	16	8	8
Staphylococcus epidermidis 270	≤0.06	≤0.06	≤0.06	≤0.06	0.25	0.25	4	4	4
Enterococcus faecium 180	2	0.25	0.5	0.5	1	1	16	0.5	8
Enterococcus faecium 180-1	0.125	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	2	1	0.5
Enterococcus faecalis 2041	0.125	≤0.06	≤0.06	≤0.06	≤0.06	0.125	4	2	1
Enterococcus faecalis 276	≤0.06	≤0.06	0.25	0.25	≤0.06	0.25	4	4	1
Enterococcus gallinarum 245	1	0.25	1	0.5	0.25	1	8	1	0.5
Haemophilus influenzae RD									>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	0.06	0.06	0.06	0.06	0.06	0.06	0.25	0.25	0.06
Streptococcus pneumoniae P1	0.06	0.06	0.06	0.06	0.06	0.06	0.25	1	0.06

TABLE 5

Organism	44	45	46	47	48	49	50	51	53
Staphylococcus aureus 446	0.125	1	1	8	>64	16	2	16	8
Staphylococcus aureus 489	0.125	2	0.5	4	32	4	2	8	2
Staphylococcus aureus 447	0.125	1	2	8	>64	>64	2	>64	16
Staphylococcus aureus X400	≤0.06	0.5	1	8	32	8	1	4	4
Staphylococcus aureus X778	≤0.06	0.5	0.5	8	32	4	1	4	4
Staphylococcus aureus 491	≤0.06	0.5	0.5	8	16	4	0.5	2	1
Staphylococcus aureus S13E	≤0.06	0.5	0.5	16	32	8	1	8	4
Staphylococcus aureus SA1199	≤0.06	0.5	1	16	32	8	2	32	8
Staphylococcus aureus SA1199A	≤0.06	≤0.06	0.125	0.5	16	4	0.5	8	1
Staphylococcus aureus SA1199B	≤0.06	0.5	1	8	32	16	2	8	16
Staphylococcus haemolyticus 105	0.25	0.5	2	8	>64	2	0.5	2	2
Staphylococcus haemolyticus 415	2	2	4	16	>64	8	2	16	8
Staphylococcus epidermidis 270	0.25	1	2	4	>64	8	1	8	4
Enterococcus faecium 180	4	0.5	0.5	0.5	64	1	0.5	2	<.06
Enterococcus faecium 180-1	≤0.06		≤0.06	1	8	2	0.25	1	0.25
Enterococcus faecalis 2041	≤0.06	0.125	≤0.06	2	8	2	0.125	2	0.5
Enterococcus faecalis 276	≤0.06	0.25	1	8	32	2	0.5	4	0.25
Enterococcus gallinarum 245	0.25	0.5	4	16	>64	0.5	0.25	1	0.06
Haemophilus influenzae RD	>64			>64	>64		>64		>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	0.06	0.06	≤0.06	≤0.06	2	2	≤0.06	1	0.06
Streptococcus pneumoniae P1	0.06	0.06	≤0.06	≤0.06	4	2	0.125	1	0.06

TABLE 5

Organism	54	55	56	57	58	59
Staphylococcus aureus 446	8	8	>64	8	32	64
Staphylococcus aureus 489	2	2	>64	2	1	32
Staphylococcus aureus 447	16	32	>64	32	>64	>64
Staphylococcus aureus X400	2	4	>64	4	4	32
Staphylococcus aureus X778	2	4	>64	4	8	16
Staphylococcus aureus 491	1	2	>64	1	1	8
Staphylococcus aureus S13E	4	4	>64	8	8	>64
Staphylococcus aureus SA1199	4	4	>64	4	16	32
Staphylococcus aureus SA1199A	2	2	>64	1	8	16
Staphylococcus aureus SA1199B	2	4	>64	4	8	32
Staphylococcus haemolyticus 105	8	2	>64	2	2	16
Staphylococcus haemolyticus 419	16	16	>64	32	>64	64
Staphylococcus epidermidis 270	8	8	>64	8	32	32
Enterococcus faecium 180	1	2	8	0.25	2	2
Enterococcus faecium 180-1	1	1	8	0.5	1	4
Enterococcus faecalis 2041	2	2	16	<.06	0.25	4
Enterococcus faecalis 276	1	4	32	0.5	0.5	8
Enterococcus gallinarum 245	1	4	8	0.06	1	1
Haemophilus influenzae RD	>64	4	>64		>64	
Escherichia coli EC14	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	1	16	8	0.06	0.06	1
Streptococcus pneumoniae P1	1	8	16	0.06	0.06	2

TABLE 5

Organism	60	61	62	63	64	65
Staphylococcus aureus 446	8	8	8	4	16	8
Staphylococcus aureus 489	1	4	2	1	8	0.5
Staphylococcus aureus 447	8	16	32	64	>64	32
Staphylococcus aureus X400	2	8	2	1	16	1
Staphylococcus aureus X778	2	4	2	1	8	1
Staphylococcus aureus 491	1	2	2	0.5	8	0.5
Staphylococcus aureus S13E	2	16	4	1	32	4
Staphylococcus aureus SA1199	2	8	2	1	16	4
Staphylococcus aureus SA1199A	0.5	1	1	0.125	4	0.5
Staphylococcus aureus SA1199B	2	16	2	1	16	2
Staphylococcus haemolyticus 109	8	1	4	1	8	4
Staphylococcus haemolyticus 415	8	8	4	32	8	32
Staphylococcus epidermidis 270	4	4	2	1	8	4
Enterococcus faecium 180	0.125	1	1	0.5	2	1
Enterococcus faecium 180-1	1	0.5	1	<.06	0.5	0.25
Enterococcus faecalis 2041	0.25	2	1	<.06	2	0.25
Enterococcus faecalis 276	0.25	2	1	0.5	2	0.125
Enterococcus gallinarum 245	0.06	1	1	0.06	2	0.06
Haemophilus influenzae RD	>64		2	>64	>64	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	0.06	1	8	0.06	2	0.06
Streptococcus pneumoniae P1	0.06	2	4	0.06	1	0.06

TABLE 5

Organism	66	67	68	69	70	71
Staphylococcus aureus 446	0.5	2	1	32	2	4
Staphylococcus aureus 489	0.25	1	0.25	32	0.5	2
Staphylococcus aureus 447	1	4	0.25	64	2	4
Staphylococcus aureus X400	0.5	1	0.125	16	1	4
Staphylococcus aureus X778	0.5	2	0.125	32	1	2
Staphylococcus aureus 491	<.06	4	0.25	16	0.5	2
Staphylococcus aureus S13E	1	4	0.5	16	1	2
Staphylococcus aureus SA1199	1	4	0.25	32	1	4
Staphylococcus aureus SA1199A	0.5	0.5	<.06	4	0.25	2
Staphylococcus aureus SA1199B	1	2	0.25	32	1	2
Staphylococcus haemolyticus 105	1	2	0.5	4	0.5	2
Staphylococcus haemolyticus 419	2	2	4	64	1	2
Staphylococcus epidermidis 270	0.5	1	0.25	4	1	1
Enterococcus faecium 180	0.25	1	1	2	1	2
Enterococcus faecium 180-1	<.06	0.5	<.06	2	0.25	0.5
Enterococcus faecalis 2041	<.06	0.5	0.125	1	0.5	0.5
Enterococcus faecalis 276	0.25	2	0.125	8	0.5	1
Enterococcus gallinarum 245	0.06	2	1	2	0.5	0.5
Haemophilus influenzae RD		1				
Escherichia coli EC14	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	0.06	4	0.06	0.25	0.125	0.5
Streptococcus pneumoniae P1	0.06	4	0.06	1	0.06	0.5

TABLE 6

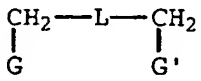
In Vitro Activity Against Enterococci		
Cpd. Number	Vancomycin Resistant Strains	Vancomycin Sensitive Strains
Vancomycin	282	3.9
A82846B	29	0.22
1	42	1.3
2	27	1.0
3	27	1.5
4	19	2.0
5	11	0.87
6	32	1.3
7	8.0	1.3
8	9.5	0.87
9	9.5	1.2
10	>90	3.0
11	38	1.7
12	4.0	0.66
13	9.5	1.2
14	>64	1.0
15	23	0.87
16	38	1.5
17	4.8	0.57
18	19	1.0
19	19	0.76
20	13	1.0
21	2.8	0.87
22	6.7	0.76
23	1.7	0.5
24	4.8	1.2
25	6.7	1.2
26	4.0	1.5
27	3.4	1.7
28	9.5	6.1
29	38	1.3
30	1.7	0.38
31	27	0.66
32	2.8	1.5
33	>128	1.3
34	53	0.87
35	>81	0.57
36	6.7	0.29
37	9.5	9.1
38	4.8	1.1
39	5.7	1.0
40	11.3	0.19
41	3.4	1.1
42	4.5	1.1
43	>128	4.6
44	76	0.66
45	2.8	0.33
46	4.8	0.17
47	2.8	1.0
48	8.0	5.2
49	2.0	1.5
50	1.7	0.44
51	3.4	2.3

TABLE 6

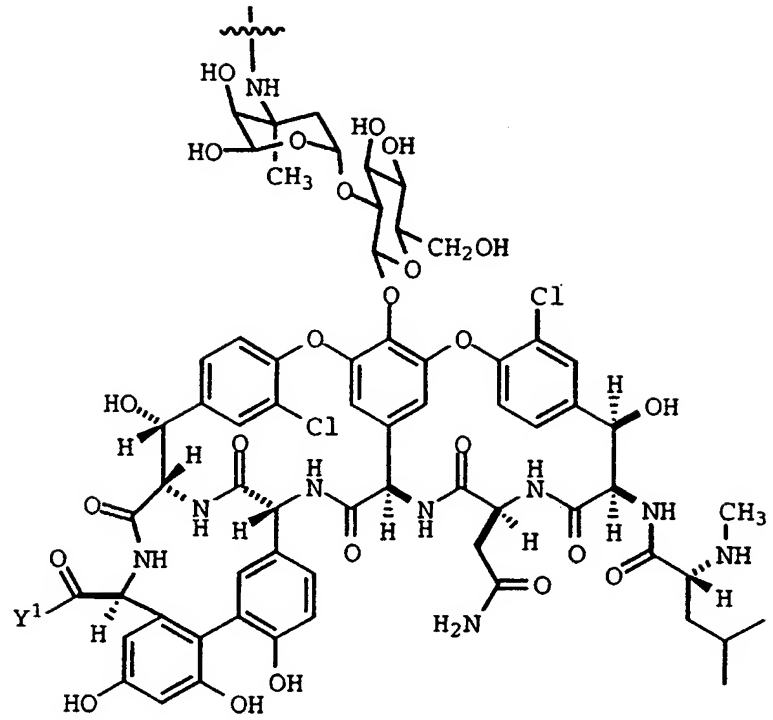
In Vitro Activity Against Enterococci		
Cpd. Number	Strains	Strains
52	4.8	0.093
53	5.7	0.66
54	4.8	2.3
55	4.8	2.3
56	8	5.3
57	11.3	0.76
58	64	1
59	2.4	1.2
60	2.4	1.3
61	2	1.2
62	3.4	1.5
63	4.8	0.57
64	6.7	4
65	22	0.57
66	2	0.38
67	3.4	0.66
68	9.5	0.25
69	5.7	2.3
70	3.4	0.38
71	2.4	0.38

Claims

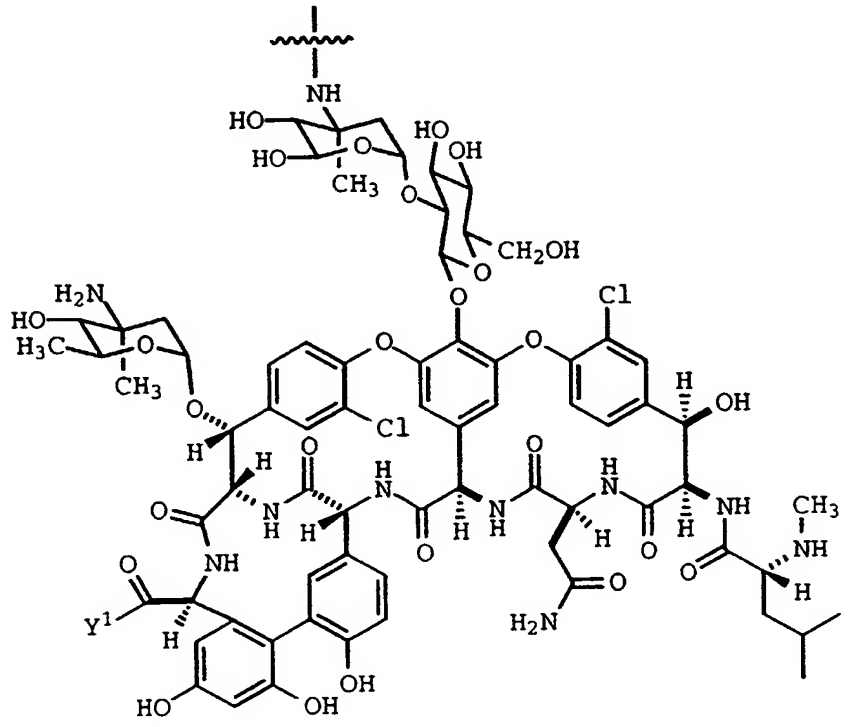
1. A compound of the formula:



wherein each of G and G' is independently deshydrovancomycin of the formula:



or deshydroA82846B of the formula:



wherein Y^1 is OH or

and Y^2 is defined as follows:

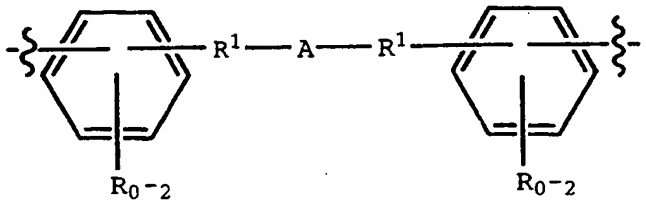
(1) each Y^2 independently represents

hydrogen,
alkyl of C_1-C_{10},
cycloalkyl of C_5-C_6,
cycloalkenyl of C_5-C_6,
naphthyl,
biphenylyl,
radical of the formula -Y^3-(Y^4)0, 1, or 2, wherein Y^3 is loweralkyl of C_1-C_6 optionally substituted by from one to three substituents, each of which is independently selected from the group consisting of halo, nitro, cyano, alkoxy, haloalkyl, and haloalkoxy; and Y^4 is

wherein each Y^5 is independently hydrogen or loweralkyl of C_1-C_4, or Y^4 is phenyl or phenyl substituted with from one to three substituents, each of which is independently
halo,
nitro,
loweralkyl of C_1-C_4,
cycloalkyl of C_5-C_6,
loweralkoxy of C_1-C_4,
haloloweralkyl of C_1-C_4, or
haloloweralkoxy of C_1-C_4; or

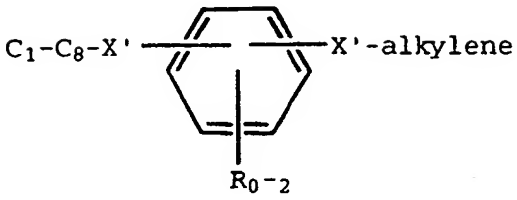
(2) one Y^2 is hydrogen and the other Y^2 is (2-furanon-3-yl); or
(3) both Y^2s are taken together with the nitrogen and constitute a five- to seven-membered heterocyclic ring optionally containing in addition to the indicated nitrogen atom one additional hetero ring atom which is nitrogen, oxygen, or sulfur, and which heterocyclic radical can be unsubstituted or substituted with from one or two substituents, each of which is loweralkyl of C_1-C_2, loweralkoxy of C_1-C_2, phenyl, benzyl, or C_1-C_6-alkanoyl; and L is a divalent linking radical of the formula A:

A.

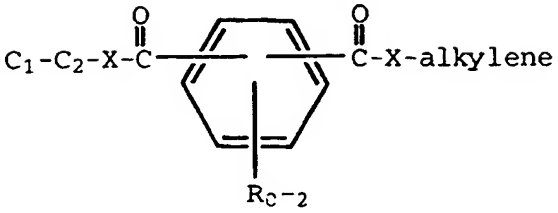


wherein A is:

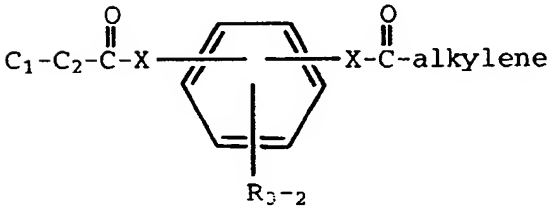
alkylene of C_1-C_{16},
(alkylene of C_1-C_4-X')$_q$-alkylene of C_1-C_4, wherein q is 1-3,
alkylene of



of C_1 -C_8;
alkylene of



of C_1-C_2, or
alkylene of

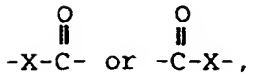


of C_1-C_2;

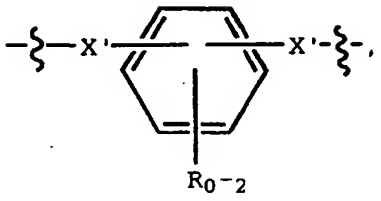
each R^1 is independently

CH_2,
O,
S,

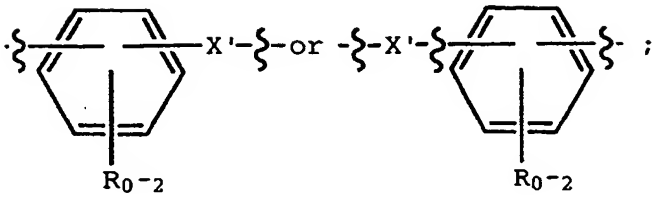
,



,



or

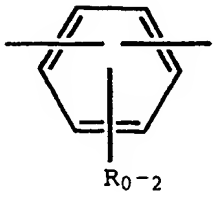


wherein each R independently represents halo, loweralkyl of C_1-C_6, loweralkoxy of C_1-C_6, phenyl, or phenyl substituted by from 1 to 2 substituents, each of which is independently halo, loweralkyl of C_1-C_6, or loweralkoxy of C_1-C_6; each X is independently -O- or

wherein R^2 is H or loweralkyl of C_1-C_4; and each X' is independently -O-, -S-, or

wherein R^2 is as defined above; or L is a divalent linking radical of the formula B:

B. -alkylene of C_1-C_8-R^3-X"-R^3-alkylene of C_1-C_8-wherein X" represents alkylene of C_1-C_4 or a phenylene of the formula



wherein R is as defined above; and each R^3 is independently CH_2 or O, or a salt thereof.

2. A compound of Claim 1 wherein both of G and G' are deshydro A82846B.

3. A compound of Claim 1 or 2 wherein L is a linking radical of formula A, A is alkylene of C_1-C_{16}, and both R^1 are O.

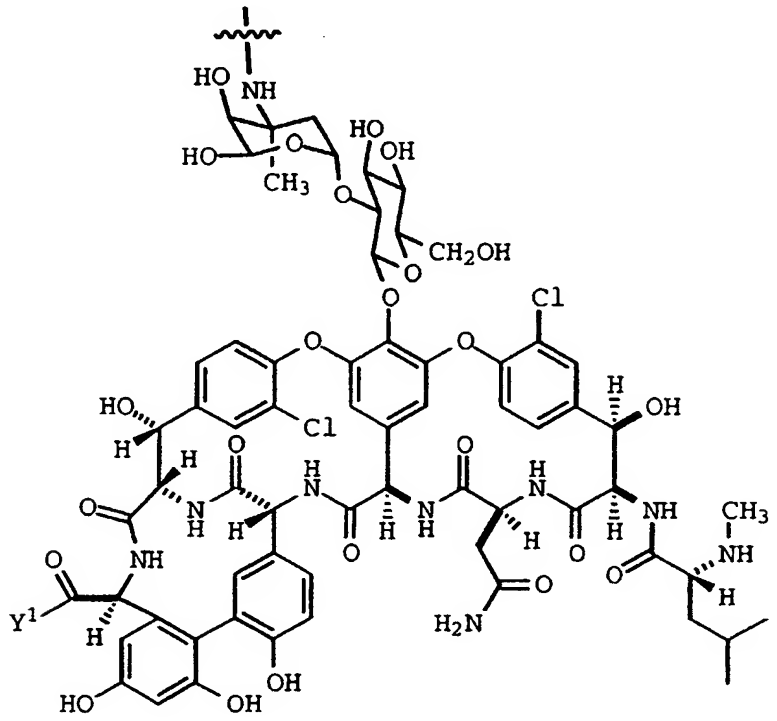
4. A compound of Claim 3 wherein A is straight-chain alkylene of C_6-C_{12}.

5. A compound of Claim 1 or 2 wherein L is a linking radical of formula A, A is (alkylene of C_1-C_4-X')$_q$-alkylene of C_1-C_4, q=2, and both R^1 are O.

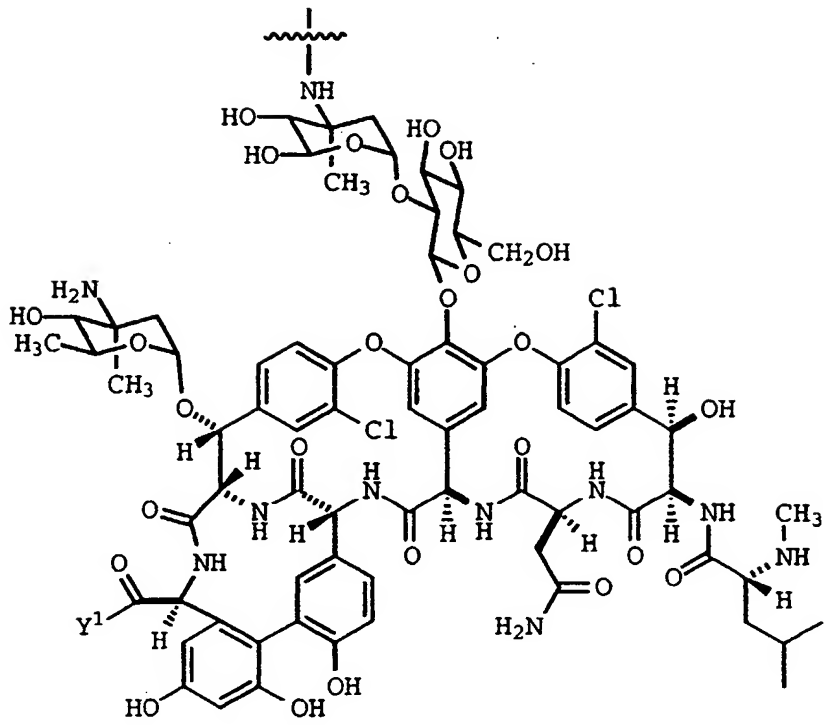
6. A compound of the formula:

G-CH_2-L-CHO

wherein G is selected from the group consisting of deshydrovancomycin of the formula:



and deshydroA82846B of the formula:



wherein Y^1 is OH or

and Y^2 is defined as follows:

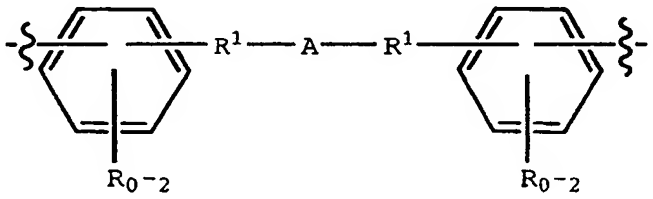
(1) each Y^2 independently represents

hydrogen,
alkyl of C_1-C_{10},
cycloalkyl of C_5-C_6,
cycloalkenyl of C_5-C_6,
naphthyl,
biphenylyl,
radical of the formula $-Y^3-(Y^4)0$, 1, or 2, wherein Y^3 is loweralkyl of C_1-C_6 optionally substituted by from one to three substituents, each of which is independently selected from the group consisting of halo, nitro, cyano, alkoxy, haloalkyl, and haloalkoxy; and Y^4 is

wherein each Y^5 is independently hydrogen or loweralkyl of C_1-C_4, or Y^4 is phenyl or phenyl substituted with from one to three substituents, each of which is independently
halo,
nitro,
loweralkyl of C_1-C_4,
cycloalkyl of C_5-C_6,

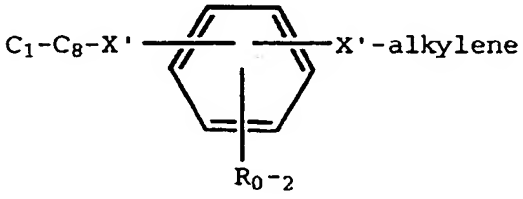
loweralkoxy of C_1-C_4,
haloloweralkyl of C_1-C_4, or
haloloweralkoxy of C_1-C_4; or

(2) one Y^2 is hydrogen and the other Y^2 is (2-furanon-3-yl); or
(3) both Y^2s are taken together with the nitrogen and constitute a five- to seven-membered heterocyclic ring optionally containing in addition to the indicated nitrogen atom one additional hetero ring atom which is nitrogen, oxygen, or sulfur, and which heterocyclic radical can be unsubstituted or substituted with from one or two substituents, each of which is loweralkyl of C_1-C_2, loweralkoxy of C_1-C_2, phenyl, benzyl, or C_1-C_6-alkanoyl; and L is a divalent linking radical of the formula A:

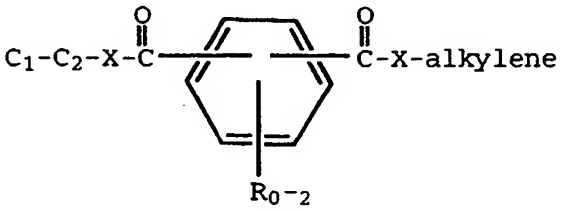
A. 

wherein A is:

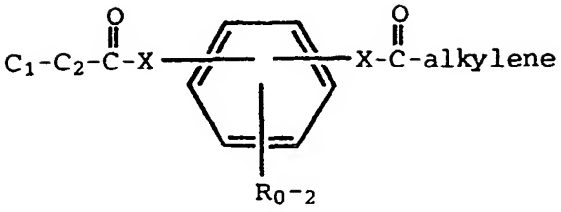
alkylene of C_1-C_{16},
(alkylene of C_1-C_4-X')$_q$-alkylene of C_1-C_4, wherein q is 1-3,
alkylene of



of C_1 -C_8;
alkylene of



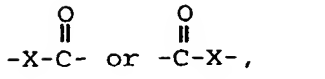
of C_1 -C_2, or alkylene of

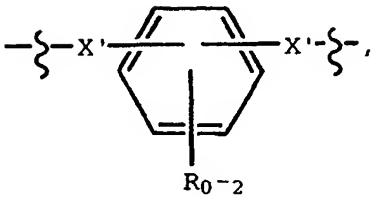


of C_1 -C_2;

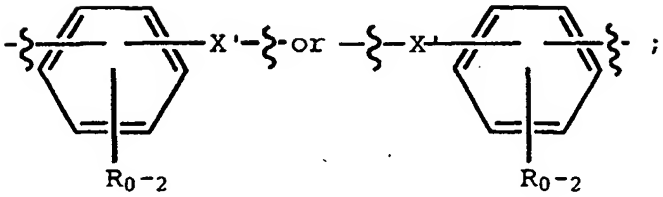
each R^1 is independently

CH_2,
O,
S,



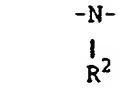


or



wherein each R independently represents halo, loweralkyl of C_1-C_6, loweralkoxy of C_1-C_6, phenyl, or phenyl substituted by from 1 to 2 substituents, each of which is independently halo, loweralkyl of C_1-C_6, or loweralkoxy of C_1-C_6; each X is independently -O- or

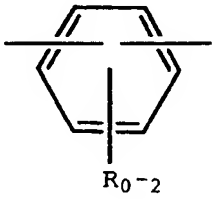
wherein R^2 is H or loweralkyl of C_1-C_4; and each X' is independently -O-, -S-, or



wherein R^2 is as defined above; or L is a divalent linking radical of the formula B:

B. -alkylene of C_1-C_8-R^3-X^*-R^3-alkylene of C_1-C_8-

wherein X^* represents alkylene of C_1-C_4 or a phenylene of the formula



wherein R is as defined above; and each R^3 is independently CH_2 or O, or a salt thereof.

7. A pharmaceutical formulation comprising a compound of Claim 1 or 6 in combination with a pharmaceutically-acceptable diluent or carrier.

8. A method of treating a bacterial infection in a host comprising the step of administering to the host an effective amount of a compound of Claim 1 or 6.

9. A method of Claim 8 wherein the bacterial infection is attributable to a vancomycin-resistant-enterococcus.

10. A compound of Claim 1 or 6 for use in antibacterial therapy.

11. A compound of Claim 1 or 6 for use in antibacterial therapy against vancomycin-resistant-enterococcus.

12. A process for the preparation of a compound as claimed in any one of Claims 1-6 which comprises reducing a Schiff base corresponding to the desired compound of Claims 1-6, and if desired, thereafter forming a pharmaceutically-acceptable salt.